UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/458,366	12/09/99	EVANS R	SALK2270-2

HM12/0706

Stephen E. Reiter
Gray Cary Ware & Freidenrich LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO CA 92121-2189

EXAMINER	
WOITACH, J	
ART UNIT	**PAPER NUMBER**
1632	9

DATE MAILED: 07/06/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/458,366	Applicant(s) Evans, R. M.
	Examiner Joseph Woitach	Group Art Unit 1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *6, 8, and 10-12* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *6, 8, and 10-12* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The amendment filed April 20, 2000 (paper number 4) has been received and entered. Claims 1-5, 7 and 9 have been canceled and claims 6, 8, 10 and 12 have been amended. Claims 6, 8, 10-12 are currently pending in the present application.

This application is a continuation in part of 09/227,718, filed 1/8/99, which is a continuation in part of application 09/005,286, filed 1/9/98, now allowed.

Specification

The disclosure is objected to because of the following informalities: The specification contains sequence listings. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

Appropriate correction is required.

For a complete response to this office action, applicant must submit the required material for sequence compliance.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6 and 8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 6 and 8 are directed to a transgenic animal. In this case, claims 6 and 8 encompass any transgenic animal, including a human being. Changing the claim to read a transgenic non-human animal would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 6, 8, 10-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for two transgenic mice wherein one mouse is a transgenic mouse whose genome comprises a transgene, wherein said transgene comprises; a) a gene which encodes a human steroid and xenobiotic receptor (SXR) polypeptide SEQ ID NO: 2, wherein said

polypeptide is characterized by; i) forming a heterodiamer with retinoid X receptor, ii) binding to a direct or inverted repeat response elements based on the half site AGTTCA, and iii) activating transcription through response elements found in steroid inducible P450 genes in response to a wide variety of natural and synthetic steroid hormones; and b) wherein said gene is operably linked to the albumin promoter/enhancer, wherein said mouse expresses said gene encoding human SXR in the liver, and wherein expression of said gene encoding SXR results in the ability of the mouse to demonstrate a response to selective steroids and xenobiotics not active in the wild type littermates and wherein the second mouse is a transgenic mouse whose genome comprises a transgene, wherein said transgene comprises; a) a gene which encodes an activated form of human steroid and xenobiotic receptor (VPSXR), wherein said polypeptide is characterized by; i) forming a heterodiamer with retinoid X receptor, ii) binding to a direct or inverted repeat response elements based on the half site AGTTCA, and iii) constitutively activating transcription through response elements found in steroid inducible P450 genes; and b) wherein said gene is operably linked to the albumin promoter/enhancer, wherein said mouse expresses said gene encoding VPSXR in the liver, and wherein expression of said gene encoding VPSXR results in growth retardation and hepatomegaly in said mouse, does not reasonably provide enablement for <u>any</u> transgenic animal expressing <u>any and all</u> polypeptides which form a heterodiamer with RXR and bind the repeat response motif half site AGTTCA.. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to practice the invention commensurate in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to a transgenic animal expressing a receptor polypeptide wherein the polypeptide is characterized by; forming a heterodiamer with RXR, binding direct repeats of the response element half site AGTTCA, and activating transcription through response elements found in P450 genes. A specific promoter operably linked to the transgene is not recited in the claim so encompasses any promoter that would 'prominently' express a transgene in the liver/intestine and any other tissue as well. Claim 12 encompasses a transgenic animal which expresses substantially no steroid or xenobiotic receptor. In the full scope of the claim as written this can be mouse expressing any transgene that has no expression of steroid nor xenobiotic receptors, however, read in light of the specification, the mouse would essentially be a mouse with a disruption in the gene encoding the steroid/xenobiotic receptor.

Breadth of claims. The claims are broad, encompassing generation any transgenic animal, and as the claim is written, any polypeptide which maintains one of the characterizations recited in the claims. Since no phenotype resulting from the transgene expression is recited, any animal simply expressing the transgene would fulfill the limitation of the claim with respect to function of the encoded receptor polypeptide. With respect to claim 12, any and all steroid/xenobiotic receptors would have to be knocked-out, or be identified as naturally occurring gene disruptions in any and all animals.

Guidance in the specification. The specification teaches specifically how to create the two mice recited in the basis of the rejection, *supra*. However, the specification is silent with respect to guidance or example for the creation of any transgenic animal. There is no guidance, nor art of record to the use of appropriate vectors, the specific promoter sequences and cloning details for all the claimed species, nor operable methods to create any transgenic animal besides the transgenic mouse. The specification is silent to if the receptor polypeptide taught in the specification will work in all species of animals, or guidance on how one would define and obtain an operable homologue from another species for the creation of that animal. Finally, the specification is silent with respect to how one would isolate or create a transgenic animal which expresses no steroid or xenobiotic receptor.

As reviewed in Evans, steroid receptors are part of a large superfamily of receptors which are activated by the binding of a steroid or in some case xenobiotic agents wherein the binding results in binding of promoter elements and activation of gene transcription (page 891; figure 2). The complex physiology of these molecules is reviewed by Beato *et al.* who conclude that 'recent developments shows that the controls of gene expression by steroid hormones is far more complex that was apparent at the time when the genes for SHRs were isolated. With more and more players getting on stage, we realize not only this complexity but also the persuasive role steroid hormones play in a vast number of physiological and pathological precesses' (pages 855-6; bridging paragraph). Manglelsdorf *et al.* described the nuclear superfamily as over 150 different proteins with a complex array of extracellular signals and transcriptional responses (page 841; first

paragraph). While the review means to stress the commonalities among various signaling pathways and that 'it is possible to consider each receptor or each hormone in isolation and to extract common themes, body physiology is rarely so simple' (page 847; bottom of column 2) and concludes that while 'the advances of the last 10 years can be viewed with satisfaction, there is still a long and challenging journey ahead' (page 484; final line). Essentially, at the time of filing of the present application, RXRs represented a growing number of superfamily members with increasingly more complex function, particularly when extended to *in vivo* physiology. The present application has defined a novel member of the SXR family of receptors and defined some of functions *in vitro* cell culture systems and *in vivo* using transgenic mice, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* who report on

transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene.

With regard to claim 12, the specification is silent on how to obtain an animal with no steroid or xenobiotic receptor. Presently, to produce an animal in which the desired gene has been disrupted, embryonic stem (ES) cells are necessary. Currently, only ES cells for the mouse are available (reviewed in Seamark and Moreadith *et al.*). Further, if methodology were available for the creation of other knock-out animals, it is not clear that such animals could be created because of the importance and complexity of RXRs in development and the normal physiology of the animal (reviewed in Beato *et al.* and Evans). The specification is silent with respect to guidance or example on how to create or identify the animal recited in claim 12. The transgenic animal in claim 12 is prophetic, besides the technical limitations of creating any animal which has a desired gene disrupted, the complexities identified for the creation of the transgenic animal apply to the creation of a transgenic animal which does not express a steroid/xenobiotic receptor. The lack of examples and specific guidance in the present application do not serve as a nexus between the complex role of RXR and the ability to express as transgenes or knock-out these molecules in all animals.

Amount of experimentation necessary. Applicants have described a prophetic transgenic animal wherein any animal would be used to express a receptor polypeptide encompassing the recited embodiments of the claim. While the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

Written Description

Claims 6, 8, 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published on December 12, 1999 in the Federal Register at Volume 64, Number 244, pp.71427-71440.

Claims 6, 8, 10-12 are drawn to a transgenic non-human animal wherein said transgenic animal one or more cells of the animal contains the nucleic acid of claim 1. The breadth of this claim would encompass transgenic and knockout type technologies, as well as chimeric animals. The specification recites general methodology one can use to create a transgenic animal (pages 84-87), however, there is no reduction to practice of any transgenic animal in the specification, nor the use of the construct to create a cell which could give rise to a transgenic mouse or any other animal. Further, no examples using ES cells are described to demonstrate that cell lines or that animals can be created which have undergone homologous recombination. The art indicates that there are multiple and different obstacles in creating transgenic animals of different species, among these are substantial variation among animals in transgene expression and variation in transgene effect due to species variation of the gene product produced.

In analyzing whether the written description requirement is met for genus claims, it is first determined were a representative number of species have been described by the complete structure. (It is not realistic to expect that the "complete structure" of a mouse, or any other animal could be described. Therefore the inquiry required by this portion of the written description guidelines is interpret to be whether the phenotypic consequences of altering a the genotype have been described). In this case, the few disclosed embodiments are not representative of the enormous number of products claimed. The claims encompass any animal, expressing a receptor polypeptide or expressing no steroid/xenobiotic receptor. Further, since expression of the transgene can be operably linked to any promoter, the claimed genus

encompasses many more possible species. The specification teaches two transgenic mice with two different forms of the SXR receptor operably linked to the albumin promoter. Each mouse exhibits substantially different phenotypes even though the SXR portion of the polypeptide expressed is essentially the same. The specification does not disclose examples of any animal created with other receptor polypeptide constructs, nor does it predict or describe how an alteration in the gene expression would affect the phenotype of the animal generated in particular other forms of the receptor polypeptide in other tissues. It is stated in the specification that SXR receptors are involved in many and multiple processes, however, there is no specific guidance on how one would create any animal with the different forms of SXR, nor is there teaching on the expected phenotypes of the resulting animal in the present application. Without even a function described for the endogenous gene, it is unclear what effect an alteration in the gene would result. This well illustrated by the expression of SXR in the two transgenic animals in the present application. While the VPSXR receptor is constitutively active and the SXR is not, it serves to illustrate how modifications to the polypeptide or expression levels can dramatically affect the phenotype in one animal.

Next, it is to be determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. It is not possible to adequately describe the claimed products because the effects of expression of a heterologous gene can not be predicted. This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of

transgenic non-human animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* who report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The specification discloses two transgenic mice with dramatically different phenotypes., has no relevant identifying characteristics. As discussed *supra*, in the enablement rejection the receptor polypeptides recited in the claims encompass a large family of genes with diverse biological functions *in vivo*. The specification has defined a nucleic acid and the corresponding encoded polypeptide, but has not demonstrated a specific biological function, nor predicted a specific function with which one could describe the phenotype of all transgenic animals expressing said nucleic acid. Since the transgenic and knock-out are encompassed in the claims, many different potential phenotypes are possible for each of these transgenic animals. Further, even if the same SXR nucleic acid is used in the transgene construct the type of promoter and site of insertion into the host genome will affect transcription of the transgene thus potentially resulting in phenotypical different animals. The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genus recited in the claims at the time of the application was filed. Thus the Applicant was not in possession of the genus of all transgenic animals which contain a polynucleotide encoding a receptor polypeptide, and is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8, 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 6, 8 and 12 are vague and unclear in the recitation of 'binding...repeat response element motif' and 'activating inducible element found in the steroid inducible P450 genes' because it is not clear to what inducible elements are being referred. The promoter of P450s have many potential transcriptional elements and because the receptor polypeptide is not specifically defined and should form a heterodiamer with RXR, the receptor polypeptide could potentially bind to all or none of the elements once the heterodiamer with RXR is formed. Further, it is not clear if the receptor polypeptide alone can activate transcription or if other elements are necessary such as the heterodiamer forming to bind transcriptional elements and activate transcription of P450 genes. Finally, as discussed above, it is not clear if the polypeptide alone can bind to the repeat response element motif.

Claims 6, 8 and 12 are vague and unclear in the recitation of 'or functional fragment thereof' because it is not clear to what specific function is being referred. The specification recites the use of functional fragments (page 22; lines 10-15), however, the specification is silent with details of specific fragments of the encoded polypeptide which are functional, or methods to

create, identify and/or assay for functional fragments of the recited SEQ ID NOs. The metes and bounds of what would constitute a functional fragment are not clearly defined.

Claims 6 and 8 are unclear in the recitation of 'prominently expressed' because it is not clear if expression is only in the liver/intestine or that the transgene can be expressed in other tissues as well. Further, the metes and bound of what is meant by 'prominently' is vague and indefinite because it clear how great of expression would constitute a prominent amount, and if prominent expression means higher than all other gene expression in the tissue or greater than the expression of the transgene as compared to tissues other than the liver/intestine.

Claims 6 and 8 are unclear in the recitation of 'is characterized by' because it makes the receptor polypeptide produced read as a product by process possessing the recited embodiments, and it is unclear if the polypeptide taught in the specification has all the recited embodiments or if there are other factors which would result in the claimed functions of the polypeptide. It is suggested language such as the polypeptide forms a heterodiamer, binds to a direct repeat, and activates transcription be substituted.

Claim 6 is unclear in the recitation of 'transgenic animal expressing a receptor polypeptide' because it is not clear if the receptor polypeptide is the transgene or that the receptor polypeptide is the endogenously encoded gene and another transgene is expressed in the animal. It is suggested to that the receptor polypeptide make reference to the fact that it the transgene expressed in said transgenic animal.

Claim 11 is unclear in the recitation of 'said cell' because it does not have antecedent basis in the preamble or in claim 10, and so it is unclear to which cell is being referred.

Claim 12 is not clear in the recitation of 'express substantially no steroid or xenobiotic receptor', because the metes and bounds of what constitutes substantially no expression is vague and unclear. It is not clear if expression is decreased or completely ablated in the whole animal or only in some tissues, or if the animal is still capable of expressing the receptor if the proper stimulation is present but no longer has constitutive levels of expression.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax number for group 1600 is 1(703)308-4242.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Joseph T. Woitach

Jasemine C. Chambers

JASEMINE CHAMBERS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600